REMARKS

FORMAL MATTERS:

Claims 1, 3-10, and 15-30 are pending after entry of the amendments set forth herein.

Claims 2 and 11-14 have been previously canceled as being directed to withdrawn subject matter.

Claims 1, 5, 9, 23 and 29 have been amended. Claims 1, 5, 9, 23 and 29 are amended to correct typographical errors. Claim 23 also is amended for proper antecedence, support for which amendment can be found in Claim 5, and throughout the specification at, for example, Figure 1, Summary, and page 16, lines 24-25.

No new matter has been added and the Examiner is respectfully requested to enter the amendments.

WITHDRAWN REJECTIONS

Applicant expresses gratitude in the Examiner's indication that previous rejections not reiterated in the present Office Action have been withdrawn.

PRIORITY

Applicant acknowledges the Examiner's confirmation that the current application claims priority to U.S. Provisional Patent Application No. 60/104,744, filed October 19, 1998.

However, the Examiner alleged that claims 1 and 23, as well as their dependent claims, do not obtain the priority date of the provisional application because the method claims recite "removing said first immobilized sequence" before step (c), and "wherein each of the first and second variable hybridization sequences is different for each subset of nucleic acid tags" in step (b) [*sic*].

Applicant respectfully submits that the Examiner is in error, and that the instant claims find full support in, and thus enjoys the priority date of, the subject provisional application.

First, support for "removing said first immobilized sequence" before step (c) can be found in the provisional application, for example, on page 15, lines 9-16, and page 16, lines 9-14. This particular example illustrates that splitting a pool of nucleic acid tags can be carried out by specific hybridization

to one of several affinity columns that each bear a different oligonucleotide or oligonucleotide analog bound to the column (e.g., first immobilized nucleotide sequence).

> An exemplary first nucleic acid-encoded split is performed by contacting, i.e. pumping a high-salt aqueous solution containing the entire pool of different nucleic acid tags cyclically over the linear sequence of affinity columns under high stringency conditions [See, e.g., Southern, EM et al., Nucl Acids Res. 22(8) 1368-1373 (1994)], using a peristaltic pump for a time sufficient for all of the specific hybridization sequences of each DNA to hybridize to the oligonucleotide or oligonucleotide analogs bound to the columns. The DNA encoded split is completed simply by breaking the luer-lock linkages between the affinity columns. At this point the different DNA tags have been divided into physically separate subsets on the basis of the specific hybridization sequence in the V region of each tag.

(U.S. Provisional No. 60/104,744, page 15, lines 9-16)

The subject provisional application further illustrates that nucleic acid tags bound to affinity columns can then be removed from the immobilizing sequences prior to a chemical reaction step.

> For example, to couple an Fmoc-protected amino-acid to the to the primary amine "chemical reaction site" which is covalently attached to the synthesis-directing nucleic acid sequence or tag, the following steps are carried out: (i) the DNA tags hybridized to the affinity columns are transferred onto columns, *e.g.*, hydroxyapatite resin columns (Bio-Rad Macro-Prep Ceramic Hyroxyapatite TYPE II catalog #1588200) with elution in 300 M CaCl or DEAE Sepharose fas (Pharmacia 17-0709-01) with elution in 10mM acetate at pH 5.0 with 0.005% triton).

(U.S. Provisional No. 60/104,744, page 16, lines 9-14)

Thus, the provisional application discloses that a nucleic acid tag hybridized to a complementary immobilized sequence can be removed from each other before a chemical reaction step (e.g., by transfer to a different column under conditions sufficient to elute the DNA tag from its complementary immobilized sequence). This aspect of the invention also is embodied, for example, in original Claims 1 and 2 of the provisional application. One of ordinary skill the art would recognize that the subject provisional application discloses and enables removing the immobilized sequence from the DNA tag prior to a chemical synthesis step as claimed.

Second, support for "wherein each of the first and second variable hybridization sequences is different for each subset of nucleic acid tags" (e.g., which language occurs in step (a) of Claims 1 and 23, and not in step (b) as cited by the Office Action) can be found in the provisional application, for example, Figure 1, on page 6, line 26 through page 7, line 2, page 12, line 31-page 7, line 2, and original claims 1 and 7.

For instance, Figure 1, in connection with its description at page 6, line 26-page 7, line 2, clearly depicts a specific example of a nucleic acid tag in which first and second variable hybridization sequences (i.e., depicted in Figure 1 horizontally as j_1-j_4, i_1-i_4, h_1-h_4 etc.) is different for each subset (i.e., depicted in Figure 1 vertically as a_1-j_1, a_2-j_2, a_3-j_3, a_4-j_4) of nucleic acid tags, where a_1-j_4 "denote distinct 20 nucleotide sequences with orthogonal hybridization properties."

> Fig. 1. depicts an exemplary DNA-directed splitting of a library of fragments. The degenerate family of DNA fragments consists of catenated 20 base-pair nucleotide sequences, which are either constant (z_1-z_9) or variable (a_1-j_4). The letters a_1 through j_4 in the variable regions of the DNA fragments denote distinct 20 nucleotide sequences with orthogonal hybridization properties. To carry out the first split, the degenerate family of fragments are passed over a set of ten different affinity resins displaying the sequences a_1^c-j_1^c, which are complementary to the sequences a_1-j_1 in the first variable region (one affinity resin is represented by the shaded ball). Ten sub-pools of the original family of fragments result.
>
> Each sub-pool is coupled to a distinct chemical monomer at the chemical reaction site. The sub-pools are recombined, and the library is split into a new set of sub-pools based on the sequences a_2-j_2, etc.
>
> (U.S. Provisional No. 60/104,744, page 6, line 26-page 7, line 2)

As also explained in the subject provisional application on page 12, line 31-page 13, line 5, "…V is an abbreviation for 'variable' and refers to the hybridization sequences which are different for each group of subsets of nucleic acid sequences."

> In one exemplary embodiment, the nucleic acid tag consists of 21 regions of twenty base pairs. Eleven of these regions are denoted C_1 -> C_{11}, wherein, C is an abbreviation for "constant" and refers to the "spacer" sequences described above. In this embodiment, the ten remaining regions are denoted V_1 -> V_{10} wherein, V is an abbreviation for "variable" and refers to the hybridization sequences which are different for each group of subsets of nucleic acid sequences. In this embodiment, every V region is bordered by two different C regions.
>
> (U.S. Provisional No. 60/104,744, page 12, line 31-page 13, line5)

This aspect of the invention also is disclosed, for example, in original Claims 1 and 7. Thus, one of ordinary skill the art would fully appreciate that the subject provisional application discloses and enables a nucleic acid tag where each of the first and second variable hybridization sequences is different for each subset of nucleic acid tags as claimed.

In view of the above remarks, Applicant respectfully submits that the claims are fully supported by, and entitled to the priority filing date of, U.S. Provisional No. 60/104,744.

CLAIM OBJECTIONS

The Examiner objected to Claims 1 and 5 for various informalities, which have been corrected by the current amendment. The objection may now be withdrawn.

REJECTIONS UNDER §112, ¶1

Rejections under 35 U.S.C. §112, first paragraph (written description)

Claims 1 and 17 are rejected under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. The rejection is respectfully traversed.

The Office Action asserts that the instant specific does not provide support for "removing said first immobilized sequence" before steps (c) and (f) of Claim 1.

In response, support for "removing said first immobilized sequence" before step (c) and (f) of Claim 1 can be found in the specification, for example, on page 15, lines 1-8, and page 16, lines 1-8. This particular example discloses that splitting a pool of nucleic acid tags can be carried out by specific hybridization to one of several affinity columns that each bear a different complementary oligonucleotide sequence (e.g., first immobilized nucleotide sequence).

> An exemplary first nucleic acid-encoded split is performed by contacting, i.e. pumping a high-salt aqueous solution containing the entire pool of different nucleic acid tags cyclically over the linear sequence of affinity columns under high stringency conditions {See, e.g., Southern, EM et al., *Nucl Acids Res.* 22(8) 1368-1373 (1994)}, using a peristaltic pump for a time sufficient for all of the specific hybridization sequences of each DNA to hybridize to the oligonucleotide or oligonucleotide analogs bound to the columns. The DNA encoded split is completed simply by breaking the luer-lock linkages between the affinity columns. At this point the different DNA tags have been divided into physically separate subsets on the basis of the specific hybridization sequence in the V region of each tag.
>
> (Specification, page 15, lines 1-8)

The specification further discloses, again by way of example that nucleic acid tags bound to affinity columns can then removed from the immobilizing sequences prior to a chemical reaction step.

> For example, to couple an Fmoc-protected amino-acid to the to the primary amine "chemical reaction site" which is covalently attached to the synthesis-directing nucleic acid sequence or tag, the following steps are carried out: (i) the DNA tags hybridized to the affinity columns are transferred onto columns, *e.g.*, hydroxyapatite resin columns (Bio-Rad Macro-Prep Ceramic Hyroxyapatite TYPE II catalog #1588200) with elution in 300 µM CaCl or DEAE Sepharose fas (Pharmacia 17-0709-01) with elution in 10mM acetate at pH 5.0 with 0.005% triton).
>
> (Specification, page 16, lines 1-8)

The specification therefore discloses that a nucleic acid tag hybridized to a complementary immobilized sequence can be removed from each other before a chemical reaction step (e.g., by transfer to a different column under conditions sufficient to elute the DNA tag from its complementary immobilized sequence). This aspect of the invention also is embodied, for example, in original Claims 1 and 2 of the current application. Thus, one of ordinary skill the art would have been apprised as to the nature of the claimed method, and how it is to be carried out with respect to removing the immobilized sequence from the nucleic acid tag prior to a chemical synthesis step as claimed.

The Office Action also asserts that the instant specific does not provide support for "a linker" for linking the chemical reaction site to the 5' terminus, as recited in Claim 17.

On the contrary, support for such a linker can be found, for example, in specification Figures 1 and 2, page 13, lines 26-29, and page 15, lines 29-31. For instance, Figures 1 and 2 illustrate a primary amine chemical reaction site linked to the 5'terminus of a nucleic acid tag through a $(CH_2)_{12}$ linker (or spacer). The specification also discloses that such linkers were well known and commercially available for such purposes, for example, a bifunctional amine-(spacer)-phosphate linker for modifying the 5'-alcohol of the 5' base of a nucleic acid tag.

> The 5' alcohol of the 5' base of the nucleic acid tag is modified with a commercially available reagent which introduces a phosphate group tethered to a linear spacer, e.g., a 12-carbon and terminated with a primary amine group (e.g., Glen Research catalog #10-1912-xx or numerous other reagents which are available for introducing thiols or other chemical reaction sites into synthetic DNA).

(Specification, page 13, lines 26-29)

The specification also discloses an example employing a primary amine functionalized linker on a nucleic acid tag for synthesis of a polypeptide, for convenience of blocking and deblocking as needed.

> For synthesis of a polypeptide on the linker substrate in the direction of carboxy to amino terminus, a free amino terminus on the linker is required that can be conveniently blocked and deblocked as needed. A preferred amino terminus blocking group is a fluorenylmethoxycarbonyl group (FMOC).

(Specification, page 15, lines 29-31)

Applicant submits that one of ordinary skill in the art, in possession of Applicant's disclosure, would have been apprised as to the nature of the claimed method, and how it is to be carried out. That the specification discloses specific examples of removing the immobilized sequence by elution and transfer of the nucleic acid tag from the immobilized sequence affinity column to another column in

exemplifying the claimed method (e.g., specification page 16, lines 1-8), or a carbon-based linker that links a primary amine chemical reaction site to the 5'alcohol of the 5' base of a nucleic acid tag by a phosphate group (e.g., Figure 1), does not detract from this basic fact. Nor does the fact that the specification exemplifies these embodiments in the synthesis of peptides with compatible reagents and conditions, namely Fmoc chemistry (See, e.g., Figure 2, and specification, page 16, paragraph 1). Thus Applicant submits that the specification and claims are in synchrony, apprising one of skill in the art as to the nature of the claimed method, and how it is to be carried out, and provides full support for "removing said first immobilized sequence" and "linker" in the context of the claimed invention.

In view of the foregoing remarks, Applicants respectfully that the rejection of Claims 1 and 17 for written description under 35 U.S.C. §112, first paragraph be withdrawn.

REJECTIONS UNDER §112, ¶2

Claim 5 is rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is respectfully traversed.

The Office Action asserts that Claim 5 fails to provide sufficient antecedent basis for "the different sequence oligomer" and "the different sequence small molecule" in step (i).

Claim 1, from which claim 5 depends, recites "the different sequence oligomer" and "the different sequence small molecule" in step (f). Claim 5 is directed to one or more additional rounds of hybridization-based splitting and chemical elaboration of compounds formed in step (f) of Claim 1, and refers to such compounds as "the different sequence oligomer" and "the different sequence small molecule" in step (i). Thus, proper antecedent basis for "the different sequence oligomer" and "the different sequence small molecule" recited in Claim 5 is provided in claim 1.

In view of the above remarks, Applicant respectfully requests that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

REJECTIONS UNDER §103(A)

Legal standard

In order to establish a *prima facie* case of obviousness, both the suggestion and the reasonable expectation of success must be found in the prior art and not in applicants disclosure. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Thus, a *prima facie* case of obviousness

requires showing some objective teaching or suggestion in the applied prior art taken as a whole would have led that person to the claimed invention, including each and every limitation of the claim as a whole, without recourse to the teachings in applicant's disclosure. See generally *In re Oetiker*, 977 F.2d 1443, 1447-48, 24 USPQ2d 1443, 1446-47 (Fed. Cir. 1992) (Nies, J., concurring); *In re Fine*, 837 F.2d 1071, 1074-76, 5 USPQ2d 1596, 1598-1600 (Fed. Cir. 1988); *In re Dow Chem. Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988).

Lerner in view of Brenner

Claims 1, 3-10 and 15-30 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Lerner et al. (US 5,573,905; 11/12/1996; herein "Lerner"), in view of Brenner et al. (US 5,635,400; 6/3/1997; herein "Brenner").

Specifically, the Examiner asserts that Lerner "teaches a method synthesizing combinatorial chemical libraries comprising various oligonucleotides and other chemical groups such as amino acids" but does "not explicitly teach using solid support immobilized complementary oligonucleotides for the "splitting" (or sorting) of the produced polymer molecules." However, the Examiner asserts that Brenner "teaches using immobilized oligonucleotides to sort or split complementary oligonucleotides" and concludes that "it would have been obvious to one of ordinary skill in the art to use the sorting method of the Brenner reference to split the polymer library of the Lerner reference."

In support for this conclusion, the Examiner alleges that one or ordinary skill (1) would have been motivated to combine the references in such a manner because Brenner teaches the advantage of using "solid substrate immobilized oligonucleotides to sort their complementary oligonucleotides for various purposes ... including automation and large-scale synthesis" and (2) would have had a "reasonable expectation of success of achieving such modifications, because the using immobilized oligomers to sort or split oligonucleotides is routine and known in the art as taught by both Brenner et al."

The rejection is traversed because while the Examiner cites Lerner and Brenner for disclosing bits and pieces of particular claims, the rejection fails to demonstrate why or how these fragmented aspects would have led one of ordinary skill to Applicant's claimed invention taken as a whole. The rejection also is traversed because the Examiner mischaracterizes many aspects of the references and claims in an attempt to reconstruct the claimed invention in hindsight.

Lerner discloses a method for making compound libraries and identifying compounds within the library that involves: (i) carrying out a 'sequential encoding' process for making a library of oligonucleotide-tagged compounds in which synthesis of each member of the library involves the alternate addition of a particular chemical unit followed by addition of an oligonucleotide sequence that is defined to "code" for that chemical unit, followed by (ii) screening the tagged compounds in the library to select those having a desired activity, followed by (iii) amplifying the selected tagged compounds having a desired activity using PCR, followed by (iv) sequencing the PCR-amplified oligonucleotide products to decode/identify the corresponding attached compound (see, e.g., Lerner Figure 2, and column 2, line 45 – column 3, line 8).

The 'sequential encoding' library synthesis step (i) of Lerner employs a four step process: (1) providing a bifunctional linker; (2) subjecting the linker to a first cycle of synthesis in which a particular chemical unit is added to one end of the linker followed by the addition of an oligonucleotide sequence that is defined to "code" for that chemical unit to the other end of the linker; (3) dividing the product into aliquots and repeating step (2) on each aliquot using a different chemical unit and oligonucleotide species that "codes" for the next added chemical unit; and (4) pooling the aliquots, dividing the pool into aliquots, and repeating steps (2)-(4) until synthesis of the library is complete (see, e.g., Lerner Figure 2, and column 9, line 56 – column 11, line 60, and Example 9).

As noted by the Examiner, no where does Lerner teach or suggest hybridization-based splitting for library synthesis, much less the specific process defined by the recited steps of Applicant's claims. In fact, the bi-functional linker (e.g., Teflon solid support derivatized with linker) that Lerner's 'sequential encoding' process begins with encodes nothing and cannot be used to pre-encode or direct the synthesis of a compound by any hybridization-based splitting strategy. Indeed, it is not until the entire 'sequential encoding' synthesis process of Lerner is completed that one ends with a nucleic acid construct that 'encodes' the compound to which it is attached.

Brenner adds nothing to Lerner. Brenner discloses minimally hybridizing nucleic acid sequences and methods of their use in various applications (see, e.g., Abstract), the relevant portion in the context of the present case being their use in making compound libraries and identifying compounds within the library. In this regard, Brenner's method involves: (i) carrying out a 'sequential encoding' process for making oligonucleotide-tagged compounds in which synthesis of each member of the compound library involves alternate additions of a minimally hybridizing nucleic acid sequence "S_k" with compound monomers "A_k" to generate a library of oligonucleotide-tagged compounds, followed by (ii) screening

the tagged compounds to select those having a desired activity, followed by (iii) sorting the tagged compounds having a desired activity by hybridization to complementary immobilized sequences, followed by (iv) sequencing the tagged compounds using a single base DNA sequencing method to identify the library compound (see, e.g., Brenner Figure 4, and column 11, line 25 – column 12, line 25).

As with Lerner, Brenner's 'sequential encoding' method of library synthesis begins with a bi-functional linker system (e.g., CPG solid support derivatized with linker) that encodes nothing and cannot be used to pre-encode or direct the synthesis of a compound by any hybridization-based splitting strategy. As also with Lerner, it is not until the entire 'sequential encoding' synthesis process of Brenner is completed that one obtains a nucleic acid construct that 'encodes' the compound to which it is attached.

Thus, Lerner and Brenner disclose essentially the same 'sequential encoding' process for making compound libraries, the difference being Brenner's use of minimally hybridizing "S_k" nucleic acid sequences as the "code" in the 'sequential encoding' synthesis process of step (i), and use of sorting in step (iii) to separate tagged compounds identified by screening of the library in order for Brenner's single base DNA sequencing method step (iv) to work. For example, without sorting/separating the individual nucleic acid species from a mixture of different sequences in a library once made, the subsequent single base DNA sequencing reaction would generate a non-interpretable blend of overlapping sequencing output, defeating the purpose of the sequencing step altogether. Brenner does not teach recombining / pooling of the sorted sequencing species prior to carrying out a next single base sequencing reaction because to do so would completely undermine the purpose of the sorting step by intermingling nucleotide species having different sequences, and thus garbling sequencing output.

Accordingly, Brenner teaches the use of immobilized oligonucleotides to sort complementary oligonucleotides after the compound library is already made and screened for hits. Indeed, Brenner explicitly states that selection, sorting and sequencing are carried out "After synthesis is completed …" (see, Brenner, column 12, line 10-25, and Figure 4)(emphasis added). In addition, Brenner teaches that the sorted species are not re-combined or pooled after the sorting step prior to carrying out a next single base sequencing reaction, otherwise the sequencing goal would be utterly and wholly destroyed. Thus it is clear that Brenner does not teach the use of immobilized oligonucleotides to sort or split complementary oligonucleotides as an integral part of a method of making the compound library to begin with. Here again, nothing in Lerner remedies the shortcomings of Brenner.

It is submitted therefore that a combination of Lerner and Brenner would have resulted in nothing more than what is disclosed in Brenner on its face, and possibly the use of PCR after the library is made and screened to amplify the selected tagged compounds having a desired activity in step (iii) of Lerner, followed by sorting the PCR amplification products by hybridization to complementary immobilized sequences according to step (iii) of Brenner, followed by sequencing of the PCR-amplified / sorted oligonucleotide products using a single base DNA sequencing method to decode/identify the corresponding attached compound according to step (iv) of Brenner.

In no instance would a combination of Lerner taken in view of Brenner have led one ordinary skill in the art to Applicant's claimed method involving steps (a)-(f) of Claim 1 (or its dependent Claims 3-10 and 15-22) or steps (a)-(m) of Claim 23 (or its dependent Claims 24-30), which requires at least one round of hybridization-based splitting, chemical synthesis and pooling of subsets of nucleic acid tags having different hybridization sequences, much less the use of pre-encoded nucleic acid tags in such a method in which each tag (1) fully encodes a compound before any chemical synthesis of the compound ever takes place, and (2) directs the synthesis of a compound to which it is ultimately attached by routing the pre-encoded tag (by hybridization-based splitting) to a particular sub-pool for a particular coupling reaction that corresponds to, and thus is pre-defined by a given combination of different variable hybridization sequences.

For instance, in contrast to what Lerner and Brenner teach regarding library synthesis in step (i) of their methods, Applicant's claimed method employs 'pre-encoded' nucleic acid tags that require absolutely no further nucleic acid sequences be added or removed when used to make a plurality of compounds per Claim 1 (and its dependent Claims 3-10 and 15-22) or Claim 23 (and its dependent Claims 24-30). All of the information for the synthesis and final synthesis product is pre-encoded in each nucleic acid tag of Applicant's method. In other words, in Applicant's method, the variable hybridization regions that dictate a given hybridization-based splitting of a pool of tags into subsets (or sub-pools) are already present in the tag, and it is the hybridization split that dictates and directs what chemical reaction is carried out on that tag in the next synthetic step, and not the addition of a new nucleotide sequence to the tag at each synthetic step as required by Lerner and Brenner.

Thus, such nucleic acid tags when employed in a method as specified to be carried out according to Claim 1 (and its dependents) or Claim 23 (and its dependents) not only encode a compound to which it is attached (i.e., compound identity), they actually direct synthesis of the compound by routing the nucleic acid tag (or tagged compound intermediate) to a specific sub-pool (via the hybridization-split)

where a selected synthesis reaction is then carried out on the tag, as opposed to merely reporting on the synthetic history of a compound as with the 'sequential encoding' method of library synthesis according to Lerner and Brenner.

The sorting process disclosed by Brenner when applied to the disclosure of Lerner has no bearing on Applicant's method, and would not have led one of ordinary skill in the art to somehow discard and then rearrange the specific teachings of the cited references to arrive at Applicant's claimed method. As noted above, Brenner teaches that the sorting step is specifically used for, and required to generate single nucleic acid species for identifying a compound in a library of compounds after it is made, because the single base DNA sequencing process of Brenner is carried out on a single nucleic acid species by a sequential, single base extension /reading process (see, e.g., Brenner Figure 4, and column 12, lines 21-24). Applicant's method is not drawn to a sequencing method, and would not be suited as a sequencing method at all given the simple fact that is carried out on a mixed population of nucleic acid tags with different sequences.

As noted above, Brenner's sequencing method requires that the sequencing process be carried out on a single template, with no mixing of that species with others having different sequences at any time in the process. To do so would destroy the purpose of Brenner's sequencing method by mixing signal output from one species with another, with no possibility of deciphering what signal came from which sequence. Even a single pooling of different template sequences from one extension reaction and then splitting them based on a completely different template sequence before carrying out a next sequencing reaction using Brenner's sequencing method would result in garbled output. This is why the sequencing aspect of Brenner's method requires a sorting step, and is what one of ordinary skill would carry at best into a combination of Lerner's method with Brenner's.

This is in contrast to Applicant's method which requires at least one round of pooling, splitting, and reacting be carried out on a mixed population of previously reacted nucleic acid tags with different sequences.

For these reasons alone, Applicant submits that Lerner taken in view of Brenner would have failed to render obvious the method according to independent Claims 1 and 23 as a whole at the time the invention was made, much less the method according to Claims 3-10 and 15-16 (which further limit Claim 1) or to Claims 24-30 (which further limit Claim 23), and respectfully requests that the rejection be withdrawn.

Lastly, Applicant also notes that the Examiner mischaracterizes Lerner and Brenner and Applicant's claimed method in an inappropriate attempt to apply disjointed fragments of these references against various other specific steps of the subject claims. Each aspect of this part of the rejection is reiterated below.

The Office Action at page 8 asserts the following regarding Lerner:

> (e.g. Abstract). The reference teaches synthesis of bifunctional molecules by attaching subunits of nucleotides and amino acids to an oligonucleotide (or nucleic acids) (e.g. Figure 2; col.13), which read on the "single stranded nucleic acid tags" as well as the method steps of forming the synthetic chemical reaction of **clms 1** and **23** as well as the amino acid subunit of **clms 19** and **26**.

First, this aspect of the rejection is irrelevant as Lerner in combination with Brenner fails to disclose the method of Claims 1 and 23 as a whole as discussed above, and thus Claims 19 and 26 which further limit Claims 1 and 23, respectively. Second, Applicant disagrees with the Examiner's characterization of the single stranded nucleic acid tags and method steps of forming the synthetic chemical reaction of Claims 1 and 23 and the amino acid subunits of Claim 19. Lerner's oligonucleotide tags are not pre-encoded; they are built by alternate additions of nucleic acid and chemical units. No where does Lerner disclose the use of fully pre-encoded nucleic acid tags. Nor does Lerner disclose any chemical synthesis step in which the nucleic acid tag is pre-encoded, much less the coupling of an amino acid to such a tag. It is simply not there.

The Office Action at page 8 asserts the following regarding Lerner:

> The reference also teaches the synthesized oligonucleotides can be extended in the direction of 3' to 5' (or 5' to 3' direction) (e.g. col. 12; col.13, lines 17+), which read on the "5' terminus is covalently attached to a chemical reaction site" (as recited in step (a) of **clms 1, 18** and **25**) with the 5'-terminal nucleotide comprising the "chemical reaction site". That is the chemical reaction of the Lerner reference is a nucleotide coupling reaction to extend the oligonucleotide at the 5' end. In addition, the terminal nucleotides in the oligonucleotides read "linkers" of **clms 17** and **24**.

This part of the rejection is irrelevant as Lerner in combination with Brenner fails to disclose the method of Claims 1 and 23 as a whole as discussed above, and thus Claims 17 and 18 (which further limit Claim 1) or Claims 24 and 25 (which further limit Claim 23). In addition Applicant disagrees with the Examiner's assertion that the nucleotide extension reaction and terminal nucleotides of Lerner

somehow reads on the subject claims. That Applicant's method employs nucleic acids that can be modified on the 5' or 3' ends with other nucleotides has no bearing on the claimed invention as a whole.

The Office Action at page 8 asserts the following regarding Lerner:

> The Lerner reference also teaches the oligonucleotide synthesis is conducted iteratively by repeating each synthesis step in cycles (e.g. Figure 2; Col.10+), which the steps read on the iterative synthesis of **clms 1, 5** and **23**.

This aspect of the rejection is irrelevant as Lerner in combination with Brenner fails to disclose the method of Claims 1 and 23 as a whole as discussed above, and thus Claim 5 which further limits Claim 1. Applicant also disagrees with the Examiner's allegation that Lerner's 'sequential encoding' method of alternate additions of nucleic acid sequences and chemical units disclosed in Figure 2 and column 10+ reads on the iterative synthesis steps embodied in Claims 1, 5 and 23. Lerner does not disclose the iterative synthesis steps embodied in Claims 1, 5 and 23, which employ pre-encoded nucleic acid tags and require hybridization-based splitting prior to each chemical synthesis reaction, followed by pooling and another hybridization-based splitting prior to the next chemical synthesis reaction.

The Office Action at the paragraph bridging pages 8-9 asserts the following regarding Lerner:

> The reference also teaches the synthesized oligonucleotides have various nucleic acid sequences (e.g. Figure 2; col.9, lines 48+; col.6, lines 26+), which read on the "variable" and "constant" hybridization sequences as well as the limitation "wherein each said first and second variable hybridization sequences is different from each subset of nucleic acid tags" of **clms 1** and **23** as well as the "at least 5 separate variable hybridization sequences" of **clm 6** as the term "variable hybridization sequences" is not specifically defined in the instant specification. The reference also teaches that the oligonucleotide can be synthesized with "all combinations and permutations of an alphabet of chemical units" (e.g. col.6, lines 26+). The reference also teaches, for example, sequences within the library that share common nucleic acid sequence while possessing variable sequences (see, for example, sequences of Figure 2), which read on the limitation of **clms 7** and **29**.

First, this aspect of the rejection is irrelevant as Lerner in combination with Brenner fails to disclose the method of Claims 1 and 23 as a whole as discussed above, and thus Claims 6 and 7 which further limits Claim 1, and Claim 29 which further limits Claim 29. Second, Applicant disagrees with the Examiner's characterization of the variable and constant hybridization sequences in the context of the subject claims. Lerner's oligonucleotide tags are not pre-encoded; they are built by alternate

additions of nucleic acid and chemical units. It is not until the entire 'sequential encoding' synthesis process of Lerner is completed that one obtains a nucleic acid construct that 'encodes' the compound to which it is attached. No where does Lerner disclose the use of fully pre-encoded nucleic acid tags, and thus tags having the variable and constant hybridization sequences as recited and taken in the context of the subject claims.

Moreover, Applicant disagrees that the "variable hybridization sequences" is not specifically defined in the instant specification. On the contrary, the specification defines variable hybridization sequence by way of example as a nucleotide sequence with orthogonal hybridization properties (see, e.g., Figure 1, specification page 6, lines 29-32, and page 12, lines 30-32). Lastly, the Examiner mischaracterizes Lerner with respect to Claims 7 and 29, which further limit the base claims from which they depend, to specify that the nucleic acid tags within each subset further comprise an adjacent constant spacer sequence separating a variable hybridization sequence from an adjacent one, with each of the constant spacer sequences being the same for all subsets of nucleic acid tags and each variable hybridization sequence being different for each group of subsets of nucleic acid tags. No where does Lerner disclose such constructs.

The Office Action at page 9 asserts the following regarding Lerner:

> The reference also teaches splitting and combining the reaction mixtures at different cycles to synthesize diverse oligonucleotides (e.g. cols 10-11), which read on the splitting and pooling steps (i.e. steps (b), (d) and (e)) of **clms 1, 5** and **23**.

This aspect of the rejection is irrelevant as Lerner in combination with Brenner fails to disclose the method of Claims 1 and 23 as a whole as discussed above, and thus Claim 5 which further limits Claim 1. The Examiner also mischaracterizes Lerner's dividing of a sample into aliquots or recombining aliquots as somehow reading on the splitting and pooling steps of the subject claims. No where does Lerner disclose any hybridization-based splitting, much less such splitting on pre-encoded nucleic acid tags, much less in the context of the claimed invention taken as a whole.

The Office Action at page 9 asserts the following regarding Lerner:

> The reference also teaches adding oligonucleotides (instead of single nucleotides) to the growing oligomers (e.g. col.14, liens 16+), which read on the **oligomer** subunits of **clm 3**. The single nucleotide reads on the "small molecule compound substituents" of **clm 4**.

This aspect of the rejection is irrelevant as Lerner in combination with Brenner fails to disclose the method of Claim 1 as a whole as discussed above, and thus Claims 3 and 4 which further limits

Claim 1. In addition, Lerner at column 14, lines 16+ is referring to building of the "code" and thus the oligonucleotide tag, not the corresponding chemical unit(s) attached therewith.

The Office Action at page 9 asserts the following regarding Lerner:

> The reference teaches using the synthesized oligomers or bifunctional molecules for subsequent PCR amplification and/or molecular binding interactions (e.g. cols 15+), which read on the intended uses of **clms 8** and **9**.

First, this aspect of the rejection is irrelevant as Lerner in combination with Brenner fails to disclose the method of Claim 1 as a whole as discussed above, and thus Claims 8 and 9 which further limits Claim 1. Second, column 15+ of Lerner is completely silent on using any enriched subpopulation of nucleic acid tags for carrying out a method in accordance with Claim 1, as required by Claims 8 and 9. On the contrary, Lerner at column 15+ is focused on determining the identifier sequence (i.e., by screening for biological activity and then sequencing those compounds having the desired activity) so as to determine a compound's identity. No where does Lerner teach employing a subpopulation of pre-encoded nucleic acid tags for any further rounds of hybridization-based splitting, chemical synthesis and pooling as required by the instant claims.

The Office Action at page 9 asserts the following regarding Lerner:

> The reference also teaches the steps of PCR amplification, subsequent restriction digestion of the PCR product, rejoining the digested strands, etc. (e.g. Figure 1; col.3, lines 60+; col.7; col.17, lines 45+), which read on the method steps of **clm 10**. The reference also teaches enriching the libraries using the PCR/restriction products for bifunctional molecules that bind to biologically active molecules (e.g. cols.17-18, bridging), which read on the enriching steps of **clms 8, 10** and **23**.

This aspect of the rejection is irrelevant as Lerner in combination with Brenner fails to disclose the method of Claims 1 and 23 as a whole as discussed above, and thus Claims 8 and 10 which further limit Claim 1. In addition, Applicant disagrees with the Examiner's characterization of what Lerner discloses. Lerner at the cited sections does not involve any compound library synthesis. Lerner Figure 1, column 3, lines 60+; column 7; column 17, lines 45+; and columns 17-18 bridging, do not read on Claims 8 or 10, which requires that the generated subpopulation be used to carry out the method of Claim 1, or Claim 23, which also can involve use of a subpopulation of nucleic acid tags for *de novo* compound synthesis by their employment in further rounds of hybridization-based splitting, chemical synthesis and pooling. Lerner does not teach employing any subpopulation of pre-encoded nucleic acid

tags for any further rounds of hybridization-based splitting, chemical synthesis and pooling as required by the instant claims.

The Office Action at page 10 asserts the following regarding Lerner:

> The reference also teaches attaching the oligonucleotide onto a solid support and then conducting further oligonucleotide synthesis (e.g. col.8), which reads on the solid support attachment of clm 16.

This aspect of the rejection is irrelevant as Lerner in combination with Brenner fails to disclose the method of Claim 1 as a whole as discussed above, and thus Claim 16 which further limits Claim 1. The Examiner also mischaracterizes Lerner and Claim 16. Lerner at column 8 does not disclose first transferring any subset of nucleic acid tags from an immobilized sequence to a solid support prior to any chemical reacting step required by Claim 16. Lerner discloses synthesis of the nucleic acid and corresponding compound on the same solid support by the 'sequential encoding' process discussed above, and that any removal from the support is carried out after synthesis is completed (Lerner, col. 8, lines 43-45). Moreover, nowhere does Lerner teach using hybridization-based splitting and thus transferring of any subset of nucleic acid tags from an immobilized sequence to a solid support prior to any chemical reacting step required by Claim 16.

The Office Action at page 10 asserts the following regarding Lerner:

> The reference also teaches attaching and removal of the FMOC protection group to the free amino acid terminus (e.g. col.5; col. 12, lines 45+), which read on the steps of clms 20, 21, 27 and 28.

This aspect of the rejection is irrelevant as Lerner in combination with Brenner fails to disclose the method of Claims 1 and 23 as a whole as discussed above, and thus Claims 20 and 21 which further limit Claim 1, or Claims 27 and 28 which further limit Claim 23.

The Office Action at page 10 asserts the following regarding Lerner:

> The reference teaches oligonucleotides with regions of at least 10 nucleotides long for both the "constant" and "variable" regions (e.g. Figure 2). The reference also teaches that making chemical polymer with various lengths (e.g. col.4, lines 35+). The reference further teaches "the length of a unit identifier oligonucleotide can vary depending on the complexity of the library..." (e.g. col.6, lines 1+). Although the reference does not explicitly teach the oligonucleotides are at least 50 nucleotides long as recited in **claims 22** and **30**, it is prima facie obvious for one of ordinary skill in the art to use oligonucleotides with various sizes (such as the ones that are at least 50 nucleotides long). Thus, depending on the experimental design and the desired polymers to be synthesized (such as the needed increase in complexity of the library), a person of ordinary skill in the art would have been motivated to use oligonucleotides with appropriate lengths to generate a combinatorial library.

First, this aspect of the rejection is irrelevant as Lerner in combination with Brenner fails to disclose the method of Claims 1 and 23 as a whole as discussed above, and thus Claim 22 which further limits Claim 1, or Claim 30 which further limits Claim 23. Second, nowhere does Lerner teach or suggest nucleic acid tags in which the variable hybridization sequences and constant spacer sequences are catenated nucleotide sequences each at least 10 nucleotides long, much less such a construct in which the nucleic acid tag includes at least 5 variable hybridization sequences. The Examiner's rational that such constructs would have been obvious to make compounds with different 'polymer lengths' misses the point of employing constant spacer regions as described in Applicant's specification, for example, as restriction sites for conducting "polynucleotide or gene-shuffling" by making new pre-encoded nucleic acid tags for carrying out the claimed methods (see, e.g., specification page 5, lines 9-10 and lines 26-31). Lerner's 'sequential encoding' method cannot be used for this purpose, as Lerner requires concurrent, alternate addition of a nucleic acid "code" with a given chemical unit.

In summary, Applicant submits that any combination of Lerner in view of Brenner would have resulted in the same 'sequential coding' etc. method taught by both references, with the exception that Brenner teaches using his minimally hybridizing nucleic acid sequences for the oligonucleotide tags (see Brenner Figure 4, and column 11, line 25 – column 12, line 25), and that any sorting by hybridization is carried out after synthesis is complete and the sorted species are not recombined as explicitly taught by Brenner (see Brenner Figure 4, and column 12, lines 11-25).

It is submitted that absent hindsight reconstruction with Applicant's specification as the guide, the cited combination of Lerner in view of Brenner would not have rendered obvious the currently claimed process. Accordingly, Applicant respectfully requests that the rejection of Claims 1, 3-10 and 15-30 under § 103(a) over Lerner in view of Brenner be withdrawn.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-390.

Respectfully submitted,
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Date: April 7, 2008

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